Risk of Hepatobiliary and Pancreatic Cancers After Hepatitis C Virus Infection: A Population-Based Study of U.S. Veterans

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Hepatitis C virus (HCV) may increase the risk of hepatopancreaticobiliary tumors other than hepatocellular carcinoma (HCC). Previous case control studies indicated a possible association between HCV and intrahepatic cholangiocarcinoma (ICC). Little is known about the association between HCV and extrahepatic cholangiocarcinoma (ECC) or pancreatic cancer. We conducted a cohort study including 146,394 HCV-infected and 572,293 HCV-uninfected patients who received care at Veterans Affairs health care facilities. Patients with two visits between 1996 and 2004 with HCV infection were included, as were up to four matched HCV-uninfected subjects for each HCV-infected subject. Risks of ICC, ECC, pancreatic cancer, and HCC were assessed using proportional hazards regression. In the 1.37 million person-years of follow-up, which began 6 months after the baseline visit, there were 75 cases of ECC, 37 cases of ICC, 617 cases of pancreatic cancer, and 1679 cases of HCC. As expected, the risk of HCC associated with HCV was very high (hazard ratio [HR], 15.09; 95% confidence interval [95% CI], 13.44, 16.94). Risk for ICC was elevated with HCV infection 2.55; 1.31, 4.95), but risk for ECC was not significantly increased (1.50; 0.60, 1.85). Adjustments for cirrhosis, diabetes, inflammatory bowel disease, hepatitis B, alcoholism, and alcoholic liver disease did not reduce the risk for ICC below twofold. The risk of pancreatic cancer was slightly elevated (1.23; 1.02, 1.49), but was attenuated after adjusting for alcohol use, pancreatitis, and other variables. *Conclusions:* Findings indicated that HCV infection conferred a more than twofold elevated risk of ICC. Absence of an association with ECC was consistent in adjusted and unadjusted models. A significant association with pancreatic cancer was erased by alcohol use and other variables. (HEPATOLOGY 2009;49:116-123.)

Hepatitis C virus (HCV) causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). The prevalence of HCV infection in the United States general population is estimated to be 1.6%, and an estimated 4.1 million infected persons live in the United States.[1] HCV infection is more common in U.S. military veterans who use the Veterans Affairs (VA) medical system, where approximately 5% are infected with HCV.[2]

Uncertainty persists over whether HCV causes cancers other than HCC, including intrahepatic cholangiocarcinoma (ICC), which is increasingly common, or extrahepatic cholangiocarcinoma (ECC). Apart from sclerosing cholangitis, risk factors for ICC are poorly understood.[3] Several case-control studies have found HCV prevalence among persons with ICC as high as 36%, with odds ratios between 2 and 17, but little or no increase in the risk of ECC.[4-7] However, these studies had limitations that precluded drawing definitive conclusions. Some studies have been too small to provide information regarding HCV's association with cholangiocarcinoma subtypes. Hospital-

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; OR, odds ratio; PPV, positive predictive value; SEER, surveillance, epidemiology, and end results.

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based studies were also subject to selection bias. We recently evaluated risk factors for ICC in a population-based case-control retrospective study using surveillance, epidemiology, and end results (SEER) and Medicare linked data and found HCV to be associated with a significantly increased risk of ICC but not ECC.[8] However, that study was limited by the possibility of ascertainment bias related to differential HCV testing between cases and controls. In one cohort study from Denmark, the risk of cholangiocarcinoma was elevated 10-fold in patients with cirrhosis; however, the study did not report the cause of cirrhosis (for example, HCV) or the whether the cholangiocarcinoma was intrahepatic or extrahepatic.[9] To our knowledge, there have been no cohort studies of HCV-infected persons to evaluate the risk of cholangiocarcinoma. Lastly, although one U.S. case-control study described a significant association between pancreatitis and HCV,[10] little is known about the association between HCV and the risk of subsequent pancreatic cancer.[11,12]

To characterize the association between HCV infection and the cholangiocarcinomas and pancreatic cancer as well as to confirm its association with HCC, we conducted a retrospective cohort study including 146,394 HCV-infected U.S. veterans—the largest cohort of HCV-infected individuals assembled to date—and 572,293 HCV-uninfected U.S. veterans. We previously examined this cohort to determine HCV infection's association with several hematological and solid organ malignancies.[13]

Patients and Methods

Data Sources. Data were collected on 718,687 inpatients and outpatients at VA medical facilities between October 1, 1988, and September 30, 2004, as previously described.[13] The institutional review boards of the National Cancer Institute and Baylor College of Medicine and its affiliated hospitals approved this retrospective study, waiving informed consent requirements and releasing health information necessary for the analysis. Sources included inpatient records from more than 150 VA hospitals in the Patient Treatment File and outpatient records from any VA facility in the Outpatient Clinic File. Both contain demographic data, encounter dates, and up to 10 diagnoses identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) codes. Patients whose outpatient visits did not include physician care or oversight were excluded. We collected information about deaths from the Beneficiary Identification Records Locator System.[14,15]

Definition of Study Cohorts. Using these sources, we identified 146,394 HCV-infected subjects and 572,293 HCV-uninfected subjects, as previously described.[13] In brief, those identified as infected had diagnosis codes specifying HCV infection (070.41, 070.44, 070.51, 070.54, and V02.62) on two visits, including one outpatient visit. The baseline date for each subject was defined as the second visit on which the HCV code was recorded. Those identified as uninfected had no HCV infection diagnosis codes in the medical record on or before the matched subject's baseline date. Inclusion criteria required uninfected subjects to be the same sex and age (± 1 year) as the matched subject, to have had a VA visit within 30 days of the matched subject's baseline date and also a prior visit, and to have their visits match in type (outpatient or inpatient) those of the matched subject with HCV. Exclusion criteria and validation tests of cohort selection are described elsewhere.[13]

Identification of Outcomes of Interest. Outcomes of interest, identified by ICD-9 code and recorded in the hospitalization or outpatient files, were ECC (156.1, 156.2, 156.8, 156.9), pancreatic adenocarcinoma (157.0, 157.1, 157.2, 157.3, 157.8, 157.9), ICC (155.1), and HCC (155.0). Only those cases of ECC, pancreatic cancer, ICC, and HCC detected 6 months after the baseline date were counted, so all calculations were based on cases diagnosed 6 months post baseline until the study's end (September 30, 2004).

To improve the specificity of this approach, we used an algorithm in defining the outcomes of interest. Specifically, we required for ECC the absence of codes for pancreatic cancer, ICC, or HCC; for pancreatic cancer, the absence of codes for ECC, HCC, or ICC; for ICC, absence of HCC; and for HCC, absence of ICC or ECC. Patients with records indicating the diagnosis of HCC, ICC, ECC, or pancreatic cancer within a year (before or after) of the HCV diagnosis date were excluded. To validate the use of our algorithm in detecting ICC and ECC, we reviewed the medical records at the Michael E. DeBakey VA Medical Center in Houston of 12 patients with ICC and 48 with ECC identified by ICD-9 codes from VA administrative datasets, as well as 29 HCV-infected cases with pancreatic cancer identified from this study's cohort and determined their classification based on a combination of clinical, radiological, and pathological criteria. Klatskin's tumors were classified as extrahepatic cholangiocarcinoma. We compared the positive predictive value (PPV) for any codes with those of the developed algorithm as outlined above. For ICC, the PPV for any code was 75% (9/12) and for our algorithm was 86% (6/7). Similarly, for ECC, the PPV for any code was 69% (33/48), and for our algorithm it was 79% (27/34). Lastly, the PPV for codes of pancreatic cancer was 70%

(17/28). We previously conducted similar validation studies for HCC.[16]

Potential Confounders. Potential confounders were also ascertained in patients with and without HCV by the presence of diagnostic codes at any time starting in fiscal year 1988 for inpatient data or fiscal year 1997 for outpatient data and the end of the study (September 30, 2004). These included hepatitis B infection (070.22, 070.23, 070.32, 070.33, V02.61), alcoholic liver disease (571.0-571.3), cirrhosis (571.2, 571.5, 571.6), alcoholism (291, 303.0, 303.9, 305.0, V0401-V0405); acute pancreatitis (577.0), chronic pancreatitis (577.1), inflammatory bowel disease (555, 556), cholelithiasis (574.0, 574.1), choledocholithiasis (574.5), choledochal cyst (751.69), or record of a cholecystectomy (51.22, 51.23). We also examined the incidence of two conditions strongly associated with tobacco smoking, namely, chronic obstructive pulmonary disease (COPD) (ICD-9: 491.2x, 493.2x, 496.xx), and lung cancer (ICD-9: 162.x) detected 6 months after baseline to examine the possibility of smoking as a potential confounder.

Statistical Analysis. We calculated incidence rates per 100,000 person-years for ICC, ECC, pancreatic cancer, and HCC by HCV status. We then compared risk in the two cohorts using Cox proportional hazards regression, adjusting for the matching factors (age, sex, baseline visit date, and type of visit). We also adjusted for race, era of military service (pre-Vietnam, Vietnam, post-Vietnam), number of inpatient and outpatient visits before baseline (a measure of use of VA medical services), and specific potential confounders for each malignancy (for example, acute pancreatitis for pancreatic cancer, and cirrhosis for ICC). We generated Kaplan-Meier curves to illustrate the cumulative incidence of ECC, HCC, ICC, and pancreatic cancer in the two cohorts (HCV-infected and HCV-uninfected) beginning 6 months after baseline.

To gauge the robustness the findings, we conducted several sensitivity analyses. First, we repeated the regression analyses including all events post baseline, not just those that occurred after the first 6 months. We also repeated the regression analyses, adjusting for potential confounders as defined only by the presence of diagnostic codes at or before the entry date into the cohort. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Baseline characteristics of the cohort, which included 146,394 subjects with HCV and 572,293 subjects without HCV (1:3.9 ratio), are presented in Table 1. All but 3.3% of the study population were men, and most subjects (56.2%) were 50 years of age or older (mean, 52 years). Most of the cohort was white; however, there were more African Americans and subjects of unknown race in the HCV-infected group. Fewer than 20% of subjects had baseline dates before fiscal year 2000, and approximately two thirds were Vietnam era veterans. The HCV-uninfected group had more annual VA hospitalizations within the 5 years before the baseline date (mean, 1.6 versus 1.2) and more outpatient visits during the previous year (mean, 19.5 versus10.8). Beginning 6 months after baseline, subjects in the cohorts were followed for a mean of 2.3 years, with a total follow-up time of 280,676 person-years in the HCV-infected cohort and 1,095,911 person-years in the HCV-uninfected cohort.

The incidence rates of ICC, ECC, pancreatic cancer, and HCC and the hazard ratios associated with HCV infection for each are presented in Table 2. Risk for ICC in the HCV-infected cohort although low (4 per 100,000

Table 1. Baseline Characteristics of Hepatitis C Virus–Infected and Hepatitis C Virus–Uninfected Veterans

Characteristic	HCV-Infected Cohort (N = 146,394)		HCV-Uninfected Cohort (N = 572,293)	
Age in years, n (%)				
< 40	5,160	(3.5)	20,416	(3.6)
40–44	18,476	(12.6)	71,740	(12.5)
45–49	41,161	(28.1)	157,787	(27.6)
50–54	45,243	(30.9)	177,085	(30.9)
55–59	18,213	(12.4)	72,750	(12.7)
60–75+	18,141	(20.9)	72,515	(12.7)
Mean age in years (SD)	51.9	(8.4)	52.0	(8.5)
Sex, n (%)				
Male	141,695	(96.8)	553,659	(96.7)
Race, n (%)				
White	76,382	(52.2)	341,181	(59.6)
African American	35,625	(24.3)	117,998	(20.6)
Other	1,221	(0.8)	6,145	(1.1)
Unknown	33,166	(22.7)	106,969	(18.7)
Baseline date, n (%)				
FY 1997-1999	25,066	(17.1)	98,799	(17.3)
FY 2000	17,036	(11.6)	66,742	(11.7)
FY 2001	23,144	(15.8)	90,084	(15.7)
FY 2002	26,025	(17.8)	101,284	(17.7)
FY 2003	27,305	(18.7)	106,431	(18.6)
FY 2004	27,818	(19.0)	108,953	(19.0)
Era of military service*				
Pre-Vietnam	15,908	(10.9)	58,272	(10.2)
Vietnam	97,332	(66.5)	358,023	(62.6)
Post-Vietnam and other	33,135	(22.6)	155,952	(27.3)
Selected comorbidities:				
Alcoholic liver disease	15,448	(10.6)	17,232	(3.0)
Alcoholism	37,665	(25.7)	101,997	(17.8)
Cirrhosis	14,187	(9.7)	9,202	(1.6)
Diabetes mellitus	8,106	(5.5)	44,021	(7.7)
Inflammatory bowel disease	1,129	(0.8)	5,445	(1.0)
Pancreatitis, acute	4,244	(2.9)	11,886	(2.1)
Pancreatitis, chronic	2,764	(1.9)	6,898	(1.2)
Cholelithiasis	6,039	(4.1)	15,020	(2.6)
Choledocholithiasis	538	(0.4)	1,602	(0.3)

*Data were missing on 19 hepatitis C virus–infected and 46 hepatitis C virus–uninfected veterans.

Table 2. Associations of Intrahepatic cholangiocarcinoma, Extrahepatic Cholangiocarcinoma, Pancreatic Carcinoma, and Hepatocellular Carcinoma with Hepatitis C Virus Infection Among Veterans

	Events/100,000 Person-Years (Events)		Hazard Ratios Comparing HCV-Infected with HCV-Uninfected Veterans		
Outcome	HCV-Infected Cohort (N = 146,394)	HCV-Uninfected Cohort (N = 572,293)	HR (95%CI) Adjusted for Matching Variables*	HR (95%CI) Adjusted for Matching Variables* and Previous VA Use	HR (95%CI) Adjusted for Matching Variables,* Previous VA Use, Race, and Era of Military Service
Intrahepatic cholangiocarcinoma	4.0 (14)	1.6 (23)	2.55 (1.31, 4.95)	2.38 (1.22, 4.65)	2.31 (1.18, 4.54)
Extrahepatic cholangiocarcinoma	4.3 (15)	4.2 (60)	1.05 (0.60, 1.85)	1.24 (0.70, 2.20)	1.25 (0.70, 2.22)
Pancreatic carcinoma	40.3 (140)	33.5 (477)	1.23 (1.02, 1.49)	1.32 (1.09, 1.60)	1.26 (1.04, 1.53)
Hepatocellular carcinoma	381.6 (1310)	25.9 (369)	15.09 (13.44, 16.94)	14.80 (13.17, 16.63)	14.75 (13.12, 16.59)

ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; VA, Veterans Affairs.

*Matching variables include age, sex, baseline visit date, and type of visit (inpatient or outpatient) for the baseline visit and a preceding visit.

person-years) was more than double that in the HCV-uninfected cohort [hazard ratio (HR) = 2.55; 95% confidence interval (CI), 1.31, 4.95] (Fig. 1A), and the risk for pancreatic cancer, although high (40 per 100,000 person-years), was less strongly but still significantly elevated in the HCV-infected cohort (HR = 1.23; 95% CI, 1.02, 1.49) (Fig. 1B). The proportion of patients with recorded cirrhosis was significantly higher (7/14, 50%) among HCV-positive ICC cases than among HCV-negative ICC (3/23, 13%). Risk for ECC was not significantly elevated (HR = 1.03; 95% CI, 0.60, 1.85) (Fig. 1C). In contrast, HCC, included as a reference measure, had the highest incidence in HCV-infected patients (381.6/100,000 person-years), reflecting a 15-fold risk (HR = 15.09; 95% CI, 13.44, 16.94) (Fig. 1D). After further adjustments for race, era of military service, and use of VA services before baseline, the point estimate of the hazard ratios for ICC did not change substantially and remained elevated

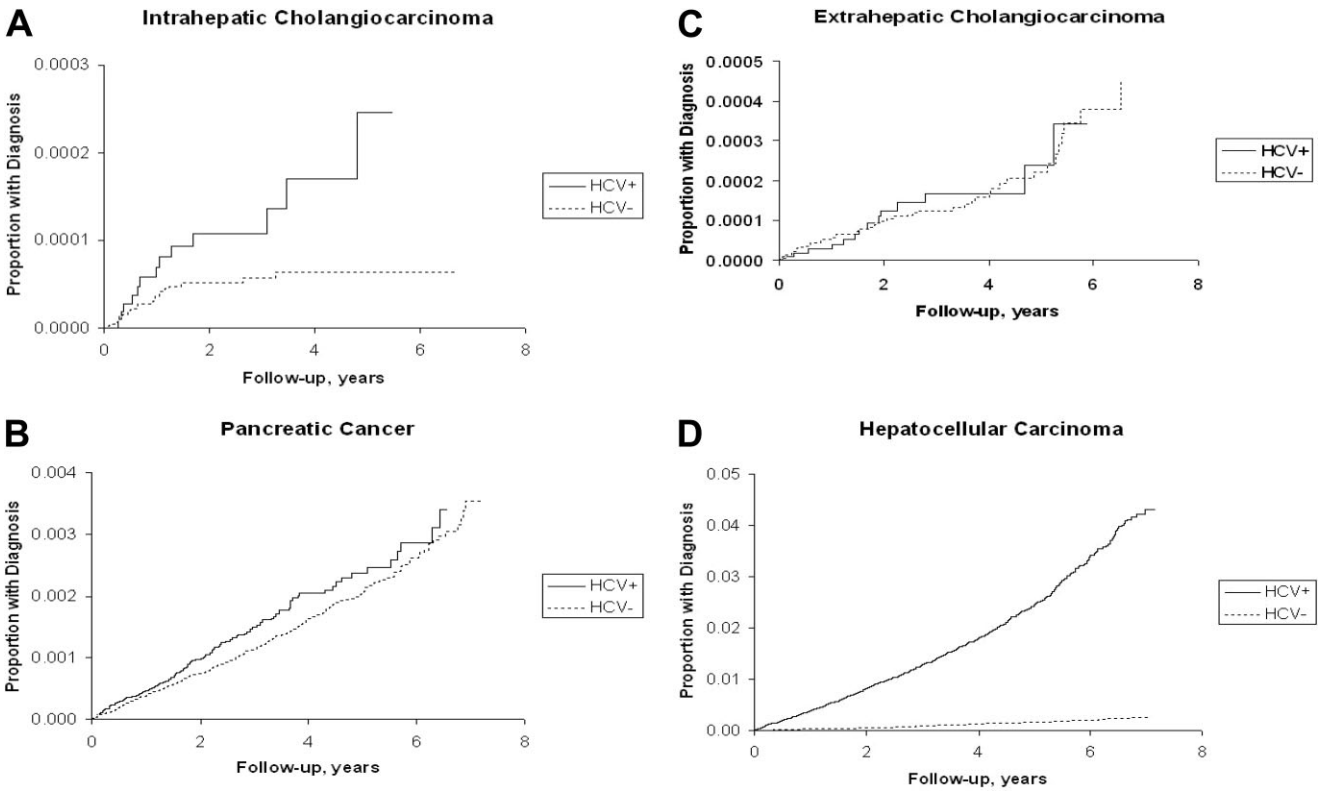

Fig. 1. (A) Kaplan-Meier estimates of the cumulative incidence of intrahepatic cholangiocarcinoma by hepatitis C virus status. (B) Kaplan-Meier estimates of the cumulative incidence of pancreatic cancer by hepatitis C virus status. (C) Kaplan-Meier estimates of the cumulative incidence of extrahepatic cholangiocarcinoma by hepatitis C virus status. (D) Kaplan-Meier estimates of the cumulative incidence of hepatocellular carcinoma by hepatitis C virus status.

Table 3. Hazard Ratios of Intrahepatic Cholangiocarcinoma, Extrahepatic Cholangiocarcinoma, Pancreatic Carcinoma, and Hepatocellular Carcinoma Among Hepatitis C–Infected and Hepatitis C–Uninfected Veterans

Variables for Which Hazard Ratios were Adjusted in Addition to Matching Variables*	Intrahepatic Cholangiocarcinoma (N = 37)	Extrahepatic Cholangiocarcinoma (N = 75)	Pancreatic Carcinoma (N = 617)	Hepatocellular Carcinoma (N = 1,679)
Matching variables only	2.55 (1.31,4.95)	1.05 (0.60,1.85)	1.23 (1.02,1.49)	15.09 (13.44,16.94)
Acute pancreatitis	2.39 (1.23,4.66)	1.02 (0.58,1.79)	1.18 (0.97,1.42)	14.97 (13.34,16.81)
Chronic pancreatitis	2.53 (1.30,4.92)	0.99 (0.56,1.75)	1.18 (0.98,1.42)	15.02 (13.38,16.86)
Alcoholism	2.49 (1.28,4.86)	1.06 (0.60,1.87)	1.21 (1.00,1.46)	14.92 (13.29,16.75)
Alcoholic liver disease	2.07 (1.03,4.16)	0.72 (0.40,1.31)	1.18 (0.98,1.44)	12.89 (11.45,14.50)
Cholecystectomy	2.55 (1.31,4.95)	1.05 (0.60,1.85)	1.23 (1.02,1.49)	15.09 (13.44,16.94)
Choledochal cyst	2.48 (1.27,4.83)	1.05 (0.60,1.85)	1.23 (1.02,1.48)	15.09 (13.44,16.93)
Choledocholithiasis	2.48 (1.28,4.83)	1.04 (0.59,1.83)	1.21 (1.00,1.46)	15.07 (13.42,16.91)
Cholelithiasis	2.45 (1.26,4.77)	0.98 (0.56,1.74)	1.18 (0.97,1.42)	14.75 (13.14,16.56)
Cirrhosis	2.76 (1.41,5.41)	0.60 (0.32,1.12)	1.12 (0.92,1.37)	12.56 (11.15,14.14)
Diabetes	2.54 (1.31,4.94)	1.04 (0.59,1.83)	1.24 (1.03,1.49)	15.13 (13.48,16.99)
Hepatitis B virus (HBV)	2.13 (1.05,4.29)	0.95 (0.53,1.71)	1.19 (0.98,1.44)	14.81 (13.18,16.63)
Inflammatory bowel disease (IBD)	2.54 (1.31,4.93)	1.05 (0.60,1.85)	1.23 (1.02,1.49)	15.10 (13.45,16.94)
Primary sclerosing cholangitis (PSC)	2.32 (1.19,4.52)	1.05 (0.60,1.86)	1.20 (0.99,1.45)	15.06 (13.42,16.91)
Diabetes + cirrhosis	2.75 (1.40,5.40)	0.59 (0.32,1.10)		
IBD + PSC	2.33 (1.20,4.55)	1.05 (0.60,1.85)		
HBV + cirrhosis	2.30 (1.13,4.68)	0.56 (0.30,1.06)		
Cirrhosis + alcoholic liver disease + alcoholism	2.20 (1.09,4.44)			

Matching variables include age, sex, baseline visit date, and type of visit (inpatient or outpatient) for the baseline visit and a preceding visit.

(HRs = 2.31-2.38). Similarly, there was no substantial change in the HR for pancreatic cancer, which also remained minimally but significantly elevated. The risk for ECC was not significantly associated with HCV after adjustment for matching variables or other factors.

To further verify our findings, we performed additional analyses adjusting for single variables or combinations of variables that might explain associations (Table 3). These analyses confirmed the strong association of HCV to ICC and HCC and the absence of an association with ECC. The association of HCV and pancreatic cancer was similar in magnitude but became nonsignificant when we controlled for variables related to alcohol (alcoholism, alcoholic liver disease, cirrhosis), pancreatitis (presence of acute or chronic pancreatitis), cholelithiasis or choledocholithiasis, hepatitis B virus (HBV), or primary sclerosing cholangitis. Lastly, we performed similar analyses with confounders, as identified in Table 3, but changing their definition to incorporate codes in the records at or before baseline; the repeat analyses produced similar findings to the ones presented above (not shown).

The incidence rates (IR) for COPD and lung cancer were very similar between the two groups with or without HCV infection (2,656 per 100,000 person-years versus 2,668 per 100,000 person-years for COPD) and (285 per 100, 000 person-years versus 293 per 100,000 person-years for lung cancer). Therefore, the incidence rate ratio was virtually equal to 1 for both conditions; 1.00 (0.98-1.03) for COPD and 0.99 (0.93-1.06) for lung cancer. Given this equal incidence of these two tobacco-smoking conditions, adjustment for these conditions in the HCV–pancreatic cancer analyses was unnecessary.

Discussion

In this cohort study of 718,687 U.S. military veterans—the largest study ever conducted on the risk conferred by HCV infection for cholangiocarcinoma—we found in 146,394 veterans with HCV infection a significant 2.55-fold increase in the risk of ICC and a 15-fold increase in the risk of HCC but no evidence that HCV infection increases the risk of ECC. A small increase (HR = 1.23) detected in the risk of pancreatic cancer could have been attributable to confounding by alcohol use or other factors.

Cholangiocarcinoma is a highly fatal cancer of the biliary tree. In the United States, approximately 5000 new cases of cholangiocarcinoma are diagnosed annually, and these cases are equally distributed between ICC and ECC.[17] Data from the SEER program indicate that the incidence of ICC tripled between 1975 and 1999 before declining slightly afterward, whereas the rates of ECC have been steady.[18]

To our knowledge this is the first time a significant association has been detected between HCV and ICC in a large cohort study. This higher level of evidence supports and extends prior observations of an association from mostly hospital-based case-control studies. In a Japanese

hospital-based study, investigators found that 36% of 50 patients with ICC but only 3% of 205 controls (other surgical patients who did not have primary liver cancer) were HCV seropositive [odds ratio (OR) = 16.87; 95% CI, 5.69, 50.00].[7] Korean investigators performed a case-control study comparing 41 cases of ICC with 406 controls without cancer and found that 13.8% of cases (3.5% of controls) were anti-HCV and 12.5% of cases (2.3% of controls) were hepatitis B surface antigen (HBsAg) positive.[6] An Italian case-control study (21 cases and 686 controls) found a positive association between ICC and HCV but not HBV.[4] In that study, the prevalence of anti-HCV was 23.1% in cases compared with 6.1% in controls. The adjusted OR for ICC was 9.7 (95% CI, 1.6, 58.9) for anti-HCV. The previous case-control studies provide consistent evidence for a statistical association between HCV and ICC; however, case-control studies risk bias by their nature. Selection bias is a problem when controls without cancer are not representative of the base population from which cases were identified, and ascertainment bias exists when cases are more likely than controls to be tested for HCV. These biases were likely present and could have skewed the results toward finding a significant association. Furthermore, the temporal relationship, the incidence rate of ICC, and the risk of ICC could not have been adequately examined with a case-control design.

Despite the doubling in relative risk, the absolute risk of ICC as measured by the incidence rate is quiet low (4 per 100,000) as compared with HCC (382 per 100,000) in this study. The only other cohort study we found showed a relatively high incidence of ICC among patients with HCV-related cirrhosis.[5] The Japanese investigators reported that 2.3% of 600 patients with HCV-related cirrhosis developed ICC during an average follow-up of 7.2 years. That study, however, had the disadvantage of lacking internal controls free of HCV infection, and, thus, it was unable to derive relative risk estimates. Therefore, in aggregate, evidence points to an association between HCV and ICC, an association supported further by our cohort study findings.

HCV is a strong risk factor for HCC, and hepatocytes and cholangiocytes have the same progenitor cell; therefore, it could be postulated that HCV could induce carcinogenesis in both cell types by the same mechanism. In at least one study, HCV RNA has been detected in ICC tissue, which further supports the potential role of HCV infection in the pathogenesis of cholangiocarcinoma.[3,19,20] Preliminary evidence indicates that HCV core protein (HCV C protein) may promote the cellular proliferation of hilar cholangiocarcinoma cells and inhibit apoptosis.[19] It may be that effects are indirect as well, with HCV damaging the liver, causing cirrhosis, and thereby increasing ICC risk. Torbenson et al.[20] reviewed 1058 cases of liver explants in patients with HCV as well as HCV-uninfected control groups; cases of chronic biliary tract disease were excluded. Dysplasia of the intrahepatic bile ducts was seen in 19 of 1058 (1.8%) of cases and was associated with chronic HCV infection and alcohol use; 10 of 19 cases (52.6%) of dysplasia were in patients with chronic HCV, and 4 of 19 (21.1%) were in patients with HCV with a history of alcohol use.[20]

Our results do not support an association between HCV infection and ECC. This study and other case-control investigations previously conducted—one hospital based[22] and another population based[6]—suggested no significant change in the risk of ECC with HCV infection. Therefore, results from all three studies are consistent and describe risk factor profiles indicating ICC and ECC as two distinct malignancies.

This is the first study to formally examine the association between HCV and pancreatic cancer. The mixed findings in this study merit additional investigation. The HRs for pancreatic cancer were consistently increased (HR: 1.23-1.32) after controlling for matching variables, previous VA use, race, and era of military service. The associations were attenuated, however, and no longer statistically significant when we controlled for variables related to alcohol use, pancreatitis, or choledocholithiasis, cholelithiasis, or primary sclerosing cholangitis. Alcohol use as well as chronic pancreatitis are known risk factors for pancreatic cancer as well as associated with HCV, and thus these factors could have been confounders of the association between HCV and pancreatic cancer. We were limited in our ability to adjust for tobacco smoking, a known risk factor for pancreatic cancer. Tobacco use is likely to be common among veterans; however, there are no to data to support unequal tobacco use among veterans based on their HCV status; such a difference would have to be present for there to be confounding. Because the diagnostic code for smoking is vastly underutilized, we did not use it for this purpose. However, we have identified two conditions strongly linked to tobacco smoking: lung cancer and COPD. We calculated the incidence rates for each condition in a similar method to that employed for the main cancer outcomes, where we considered only cases diagnosed 6 months or longer than the index date for HCV. The incidence rates for these two conditions were very similar between the two groups with or without HCV infection, and therefore adjustment for these conditions in the HCV–pancreatic cancer analyses was unnecessary.

The biological reason for an association between HCV and pancreatic cancer is unclear. A previous report found

that patients diagnosed with acute hepatitis C also suffer from acute pancreatitis.[10] In addition, serum levels of pancreatic enzymes have been shown to increase with the progression of liver disease in patients diagnosed with viral hepatitis.[11,12]

Findings in this study also confirmed the high risk of HCC conferred by HCV infection (HR = 15.09). These are consistent with findings of a published meta-analysis, in which the pooled odds ratio from 32 case-control studies was 17.3 (95% CI, 13.9-21.6) for anti-HCV/HCV RNA positivity in the setting of HBsAg negativity,[22] and confer internal validity to the study. We did not examine HBV in the current study because we have previously shown that HBV-related ICD-9 codes are poorly predictive of the serological status in the medical record.[23]

Strengths of the study include its large sample size and relatively long follow-up, which allowed the examination of otherwise rare malignancies. The study examined users of the VA health care system, which tends to be relatively stable and provides standardized access to veterans, independent of socioeconomic status. Use of an HCV infection-free veterans population as an internal control group, rather than the general population, was meant to ensure the comparability of the two groups with regard to features other than HCV. In addition, we conducted internal checks, including tests of the predictive value of codes used to denote HCV infection,[13] and the careful verification of outcomes of interest—ICC and ECC—through a limited individual chart review. This review validated the use of logical algorithms to identify these conditions as well as adding assurance about the codes themselves. We previously conducted a similar chart validation study for HCC and reported a PPV of 94%.[16]

In the analyses, we obtained consistent results after considering a broad range of confounders, which encourages confidence in our findings. Efforts were made to clearly establish the existence of HCV infection before diagnosis of malignancy, and therefore we considered only cancers diagnosed 6 months after the HCV index date. Furthermore, in additional testing, the risks of several negative control cancers, including prostate cancer, colon cancer, and melanoma, which have no plausible relation to HCV infection, were not elevated, confirming the reliability of our database.[13]

Limitations to our study are in general those imposed by work with administrative datasets. Reliance on ICD-9 codes and large administrative databases for identifying HCV infection was necessary because laboratory data are not collected systematically nationwide. Although our internal chart review study validated this approach, some misclassification was still present given that only a small proportion of cancer cases were diagnosed in the single center where the chart review was conducted. Other factors that may have affected our results include the reality that cancer rates are higher in veterans than in the general population,[24,25] the study group was overwhelmingly male, and exclusive reliance on VA records fails to capture all outcomes. Other limitations included the possibility of differential ascertainment of potential confounders in cancer cases versus non-cases. However, when we conducted a sensitivity analysis that considered only confounders present at baseline, the results were similar to those in the primary analysis. Lastly, we did not capture cancer outcomes that were diagnosed outside the VA. The potential effect of missing information is difficult to predict.

In conclusion, among 146,394 HCV-infected U.S. military veterans, we found a 2.55-fold elevated risk of ICC. Our study is the largest epidemiological study ever conducted to evaluate the relationship between HCV and ICC, ECC, and pancreas cancer. We adjusted our analyses for multiple confounding variables and found that the relationship between HCV and ICC remained significantly positive and that the association between HCV and ECC remained negative. Results also suggested a possible relationship to pancreatic cancer that requires further study.

These findings associating HCV and ICC but not ECC support those of prior smaller epidemiological studies as well as previously described carcinogenic mechanisms related to HCV infection. From a clinical perspective, early intervention strategies, including screening HCV-positive individuals earlier or more rigorously, may improve the outcomes for both HCC and ICC. Additional epidemiological studies of ICC are needed, and new evaluations of the effects of early interventions, including HCV treatment, on the molecular carcinogenesis of ICC are warranted.

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